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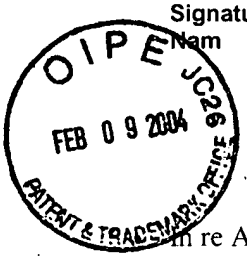

Attorney Docket No. 7381

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Edwin F. Ullman, *et al.*

Serial No.: 09/691,383 Art Unit: 1641

Filed: October 17, 2000 Examiner: Lisa V. Cook

Title: Simultaneous Screening of Multiple Analytes

MS Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TRANSMITTAL LETTER

Transmitted herewith for filing in the above-entitled patent application are the following:

1. Appeal Brief (21 pages) (in triplicate)
2. Transmittal Letter (in duplicate)
3. Return postcard

Deposit Account Authorization

[X] The fee for filing this Appeal Brief is $330.00 (37 CFR 1.17(c))
[X] Please charge $330.00 to Deposit Account 04-0010.
[X] Please charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 04-0010. A duplicate copy of this Transmittal Letter is enclosed.

Address for Correspondence

Please continue to address all correspondence for this application to **Susan Yarc, Behring Diagnostics GmbH, c/o Dade Behring Inc., 1717 Deerfield Road, Deerfield, Illinois 60015-0778, whose telephone number is (847) 267-5364.**

Respectfully submitted,

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PATENTS
Attorney Docket No. 7381

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application: 09/691,383

Inventors: Edwin F. Ullman, *et al.*

Filed: October 17, 2000

Title: Simultaneous Screening of Multiple Analytes

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANTS' BRIEF ON APPEAL

This is an appeal from the Final Rejection in the Office Action dated July 14, 2003, by the United States Patent and Trademark Office (the "Office") in the above-identified patent application. A Notice of Appeal was mailed on December 5, 2003.

Jurisdiction over this appeal resides in the Board of Patent Appeals and Interferences under 35 U.S.C. §134.

An oral hearing was not requested.

REAL PARTY IN INTEREST

The real party in interest is Dade Behring Marburg GmbH.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

The claims for consideration on appeal in the present application are Claims 19-34. Claims 1-18 were withdrawn from consideration and were canceled in Appellant's Amendment under 37 C.F.R. §1.116 mailed September 8, 2003. Claim 19 was amended in an Amendment under 37 C.F.R. §1.111 mailed on May 1, 2003. Claims 20-34 are originally filed. The claims as amended are presented herewith in the attached Appendix to Appeal Brief.

STATUS OF THE AMENDMENTS

In an Advisory Action mailed November 13, 2003, the Office indicated that the amendments made to the claims in Appellant's Amendment under 37 C.F.R. §1.116 would be entered.

SUMMARY OF THE INVENTION

The present invention is directed to methods for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of such drugs (p 4, ln 19-20 where p = page and ln = line(s) of the present specification). The sample and an antibody for each of the drugs are combined in a medium (p 9, ln 14-16, and p 10, ln 23). To this combination is added, for each of the drugs, a first reagent comprising a first label, a small molecule and a drug analog (p 11, ln 4-8, p 11, ln 26-27, p 11, ln 26-27). The drug analog competes with the drug, if present, for binding to the antibody for the drug (p 11, ln 18-20). A second reagent is added to the combination where the second reagent comprises a second label and an antibody for the small molecule (p 15, ln 24-28). The first label and the second label interact in close proximity to produce a predetermined increased amount of signal if one or more of the drugs are present in the sample (p 17, ln 3-7). The antibody for the drug binds to the drug analog of the first reagent thereby inhibiting the binding of the antibody for the small molecule to the small molecule (p 27, ln 9-23). The medium is examined for the amount of the signal where a predetermined increased amount of signal is related to the presence of one or more of the drugs in the sample (p 17, ln 7-11).

As indicated in the present specification, high volume screening for drugs of abuse is currently carried out commercially by conducting a series of individual homogeneous immunoassays (EMIT or FPIA). A cut off level is set for each drug, which is used to establish whether a particular result will be defined as positive or negative. It is necessary for testing laboratories to handle separate reagent sets and carry out separate assays for each of the commonly abused drugs in every sample. Typically, the presence of as many as six drugs must be determined. (p 1, ln 22-28)

The present invention permits effective screening of samples for the presence of one or more of a plurality of different analytes (p4, ln 19-20). For example, the present invention provides for screening a sample for one or more of a plurality of drugs of abuse where one is attempting to ascertain whether a sample contains any of the plurality of drugs. For example, one may be interested in determining whether a sample contains one or more of cocaine and morphine. (Example 1 beginning on p 49) In accordance with this exemplary embodiment of the present invention, the sample to be tested is combined in a medium with an antibody for each of the drugs of interest. Accordingly, antibodies for each of cocaine and morphine are added to the medium along with the sample. Also added to the medium, for each of the drugs, is a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog, wherein the drug analog competes with the drug, if present, for binding to the antibody for the drug. Thus, multiple first reagents are added to the medium, one each for each of cocaine and morphine. Also added to the medium is a second reagent comprising (i) a second label and (ii) an antibody for the small molecule, wherein the first label and the second label interact in close proximity to produce a predetermined increased amount of signal if one or more of cocaine and morphine are present in the sample. A single second reagent is added for all of the drug analytes of interest in the sample. The medium is examined for the amount of the signal and a predetermined increased amount of signal is related to the presence of one or more of cocaine and morphine in the sample. The above example is by way of illustration and not limitation.

ISSUES

I. Whether the final rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b) should be reversed?

II. Whether the final rejection of Claims 21 and 22 under 35 U.S.C. §103(a) should be reversed?

III. Whether the final rejection of Claims 27-34 under 35 U.S.C. §103(a) should be reversed?

GROUPING OF CLAIMS

Appellant submits that Claims 19-20 and 23-26 stand or fall together as to the rejection under 35 U.S.C. §102(b).

Appellant submits that Claims 21 and 22 stand or fall together as to the rejection under 35 U.S.C. §103(a).

Appellant submits that Claims 27-34 stand or fall together as to the rejection under 35 U.S.C. §103(a).

ARGUMENT

I. Whether the final rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b) should be reversed?

A. The Rejection

Claims 19-20 and 23-26 were rejected under paragraph (b) of the above code section as being anticipated by Oh, *et al.* (U.S. Patent No. 5,851,778 and WO 89/03041) (collectively, Oh). The above disclosures are essentially duplicative and will be addressed herein collectively as Oh.

The Office asserts that in both the cited references Oh employs a conjugate that comprises three moieties or members to evaluate specific binding partners. Two members of the conjugate are relatively small molecules (less that about 7,000 Daltons). When the conjugate is bound by a macromolecular specific binding partner (sample drug-analyte), it sterically inhibits the binding of other/different macromolecules to another member of the

three-member conjugate. In support of this position, the Office refers to the abstracts of Oh.

An assay protocol, continues the Office, is outlined in figure 1 of both references wherein the assay employs a tridentate complex (referred to by the Office as a first reagent) comprising biotin (first label), first hapten (drug analog), and second hapten (small molecule). The complex is mixed with a sample (free analyte – first hapten/drug), avidin (second label), antibody to the first hapten (antibody to the drug), and an antibody to the second hapten (antibody to the small molecule). The Office further contends that both references evaluate the signal from the target molecules as an increase over background or control signals (predetermined signals).

B. Standard of Rejection

In order to maintain a rejection under 35 U.S.C. §102(b) the Office must first establish a *prima facie* case of anticipation. An invention is anticipated if each and every limitation of the claimed invention is disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994). It is not enough, however, that the prior art reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention arranged in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 U.S.P.Q. 481 (Fed. Cir. 1984). In addition, the allegedly anticipating reference must be enabling and describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art. *In re Paulsen*, *supra*, at 1673. The anticipation determination is viewed from one of ordinary skill in the art. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

C. Application of Standard to the Claims

(1) Scope and Content of the Art

Oh discloses a trifunctional conjugate having three chemical moieties attached through a spacer moiety. At least two of the chemical moieties are relatively small molecules. The spacer moiety is selected to impart certain steric properties to the conjugate. In one embodiment the binding of a macromolecular specific binding partner to one of the chemical moieties sterically inhibits the binding of a different macromolecule to another chemical moiety. In another embodiment the binding of a first chemical moiety to a macromolecule restricts the subsequent binding of a second chemical moiety to a proximate location on the same macromolecule. The three chemical moieties are preferably a nitrophenylazido residue, a phenyl boronic acid residue and a solid support or a label such as biotin. The spacer is preferably cysteine, lysine, glutamic acid, pyroglutamic acid, S-acetylmercaptosuccinic anhydride or ω-carbobenzoxylysine. The conjugate is used in immunoassays and for targeted labeling of proteins. In an assay, a sample is contacted with the conjugate, a limited quantity of analyte binding partner and an excess of small molecule binding partner. Presence of the analyte is determined by detecting the amount of analyte binding partner diverted away from analyte attached to the spacer of the conjugate.

(2) Differences between the Art and Claims 19-20 and 23-26

Oh's assay is directed to the determination of a single analyte in a sample using only reagents for the detection of a single analyte. On the other hand, the present invention is directed to an assay for the determination of one or more of a plurality of drugs of interest in a sample. The present methods include the step of adding multiple antibodies, one each for each of the drugs suspected of being in the sample. Additionally, the present methods include the step of adding multiple first reagents, one each for each of the drugs suspected of being in the sample.

As can be seen, for instance, from Oh's examples, the patentee conducts assays for a single analyte (e.g., theophylline or theophylline-amine) using only reagents for the detection of such single analyte. See, for example, column 37, lines 34-48, in which an aliquot of the patient's sample is combined with an aliquot of the tridentate solution. The

combined solution is then incubated with the optimized antibody solution. Then, an aliquot of the optimized proximity label solution is added. After inclusion of the substrate solution, signal is measured. The patentee indicates that the same procedure is repeated for various dilutions of a theophylline or theophylline-amine standard. In this way, continues the patentee, a standard curve is obtained and the concentration of theophylline or theophylline-amine in the sample can be extrapolated.

(3) Argument

As indicated above, Oh does not disclose each and every element of the claimed invention of the above claims. One skilled in the art, reading the disclosure of Oh, would not be placed in possession of a method such as claimed in the present application. The skilled artisan would recognize the significant difference between Oh's method of detecting a single analyte versus the method of the invention wherein a sample is screened for the presence of one or more drugs using multiple reagents, one set of reagents for each of the drugs suspected of being present in the sample. As the court has held, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention (*Scripps Clinic & Research Found. v. Genentech Inc.*). This is not the case in the present situation.

The Advisory Action particularly focused attention on Appellant's statement that Oh does not disclose or suggest adding multiple antibodies, one each for each of the suspected analytes. The Advisory Action contended that Oh teaches the use of two antibodies (multiple antibodies) in Oh's assay of figure 1, namely, an antibody to a first hapten and an antibody to a second hapten.

However, Appellant's argument was that Oh does not disclose or suggest adding multiple antibodies, one each for each of the drugs. Oh does not teach such a method and reagents. Oh's assay, to which the Advisory Action referred, uses an antibody to a first hapten and an antibody to a second hapten. Nowhere does Oh disclose multiple antibodies, one each for each of the drugs suspected of being in the sample. Oh indicates that the first tridentate member is biotin, the second tridentate member is a first hapten, which is identical to the analyte of interest, and the third tridentate member is a second hapten

different from the analyte of interest (column 15, last line, to column 16, line 6). Accordingly, in the example shown Oh uses only one antibody for an analyte, which is in keeping with his teaching of an assay for the detection of a single analyte, not one or more of a plurality of analytes. Oh does not disclose using multiple antibodies, one each for the detection of multiple suspected analytes, as claimed by Appellant.

The Advisory Action asserted further that the features upon which Appellant relies (i.e., multiple drug detection with multiple antibodies) are not reflected in the claims. The Advisory Action further contended that the instant claims read on not just multiple drug detection but also on single drug detection (one or more drugs in a sample).

Appellant respectfully disagrees with the position of the Advisory Action. The instant claims recite in the preamble "determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs." (emphasis added) Furthermore, the body of the claim recites "(a) combining in a medium said sample and an antibody for each of said drugs, (b) adding to said combination, for each of said drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog." (emphasis added) In this way, Appellant's method screens a sample for the presence of one or more drugs in a sample suspected of containing a plurality of drugs to determine if any of such drugs are in the sample. Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of analytes of interest in a sample. Oh does not disclose or suggest adding multiple antibodies, one each for each of the suspected analytes. Oh fails to disclose or suggest adding multiple first reagents, one each for each of the suspected analytes. Accordingly, Oh does not teach an assay for the determination of one or more drugs in a sample suspected of containing any of a plurality of the drugs. As mentioned above, anticipation requires the presence, in a single prior art reference disclosure, of each and every element of the claimed invention arranged in the claim (*Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., supra*). The teaching of Oh falls far short of this required level of disclosure.

As can be seen from the above analysis, the assertion in the Advisory Action that the features upon which Appellant relies are not recited in the claims is misplaced. The features relied on are recited in the present claims as discussed above and there is no need

to read limitations into the claims from the specification. Accordingly, *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993) is not applicable to the present situation.

The Advisory Action further argued that, even though every limitation of a claimed process is not disclosed in a prior art reference, anticipation can be found on the inferences which one skilled in the art would reasonably expect to draw therefrom. The Advisory Action also referred to Oh at column 16, lines 30-49, as teaching that other drugs can be effectively assayed in competition by the Oh method. However, the cited passage does not teach an assay as presently claimed, which involves combining a sample with an antibody for each of the drugs suspected of being in the sample and adding to the combination, for each of the drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog. Oh is merely indicating that his approach may be used to assay for a drug other than theophylline.

Oh's use of the term "competitively" must be viewed in context. The language of Oh that recites "in a competitively modulated assay such as NIIA" would not be interpreted by one skilled in the art beyond what is taught by Oh. At column 15, lines 21-25, Oh indicates that the tridentate is particularly useful in competitively modulated assays where the analyte of interest is a hapten, or analog thereof. The competitively modulated assay to which Oh refers is also discussed at column 14, lines 36-57, and column 15, lines 14-21. It is readily seen that the use of Oh's tridentate involves steric hindrance or inhibition. The binding of a macromolecule to the second (modulating) member of the tridentate prevents the simultaneous binding of the first and/or third tridentate members to their corresponding macromolecules. In this way, Oh's method is applicable in the area of competitively modulated immunoassays. For the reasons given above, Oh does not teach that "other drugs can be effectively assayed in competition."

D. Conclusion

Appellant has demonstrated above that the rejection of Claims 19-20 and 23-26 as anticipated by Oh cannot be sustained. The Oh references do not disclose each and every element of the claimed invention as explained above. At the very least, Oh does not

disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs.

II. Whether the final rejection of Claims 21-22 under 35 U.S.C. §103 should be reversed?

A. The Rejection

Claims 21 and 22 were rejected under 35 U.S.C. 103(a) as being unpatentable over Oh in view of Maggio (Enzyme Immunoassay, CRC Press 1980, pages 186-187). The Advisory Action argued that Oh differs from the instant invention in not specifically teaching the detection assay employing a solid phase such as particles. However, asserted the Advisory Action, Maggio discloses enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase. The Advisory Action concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use solid phase/particles as taught by Maggio in the assay method to detect the drug interaction of Oh.

B. Standard of Rejection

In order to maintain a rejection under 35 U.S.C. §103 the Office must first establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification. *In re Lintner*, 458 F.2d 1013, 173 U.S.P.Q. 560 (C.C.P.A. 1972). In asserting a *prima facie* case of obviousness involving more than one reference, the Office must show some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references offered by the Office as evidence of obviousness. *In re Lalu*, 747 F.2d 703; 223 U.S.P.Q. 1257 (Fed. Cir. 1984). In determining the scope and content of the prior art, references must be considered in their

entirety, as a whole, including portions that would lead away from the claimed invention. *In re Panduit*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed Cir. 1987). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine, supra.*

C. Application of Standard to the Claims

(1) Scope and Content of the Art

The disclosure of Oh is set forth above. Maggio teaches separation steps with special reference to solid phases including beads. The reference indicates that, in virtually all of the enzyme-immunoassays discussed in the reference, either the antigen or antibody may be immobilized onto a solid phase. The solid phase can be in the form of particles or preformed into discs, tubes, beads or microplates. Maggio indicates that the advantage of a preformed solid phase is that washing can be carried out very easily whereas, in contrast, washing of particulate solid-phase materials necessitates centrifugation that can be inconvenient.

(2) Differences between the Art and Claims 21-22

Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of drugs of interest in a sample using multiple sets of reagents, one set for each of the suspected plurality of drugs. Oh does not disclose or suggest the step of adding multiple antibodies, one each for each of the suspected drugs. Oh fails to disclose or suggest the step of adding multiple first reagents, one each for each of the suspected drugs. Maggio discloses the use of particles in immunoassays but does not teach or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of adding multiple first reagents, one each for each of the suspected drugs.

(3) Argument

Oh and Maggio, either individually or in combination, do not teach or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of

adding multiple first reagents, one each for each of the suspected drugs. Therefore, a combination of the teachings of the two references cannot result in the presently claimed methods. Furthermore, even if for the sake of argument the combined teachings could result in the presently claimed methods, Maggio teaches away from making the combination suggested in the Advisory Action. As mentioned above, Maggio teaches the preference for a preformed solid phase over a particulate solid phase. Therefore, the skilled artisan, if inclined to make a combination of teachings, would be inclined to use discs, plates and the like, rather than particles, in the method of Oh. In any event, as mentioned above, the combined teachings of Oh and Maggio do not produce the presently claimed methods because the combined teachings still do not contain all of the elements of the presently claimed methods.

As mentioned above, in determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification (*In re Lintner*, *supra*). The teaching of Oh and Maggio fall far short of this required level of disclosure. Oh does not disclose assaying for the presence of one or more of a plurality of drugs in a sample and, thus, using particles in the method of Oh does not result in the methods of Claims 21 and 22.

Furthermore, as mentioned above, in determining the scope and content of the prior art, references must be considered in their entirety, as a whole, including portions that would lead away from the claimed invention (*In re Panduit*, *supra*). In the present situation, it would not be unreasonable for the skilled artisan to conclude that Maggio actually does teach away from the methods of the invention of Claims 21 and 22.

Appellant previously submitted that it has been held that there must be some suggestion, motivation or teaching in the prior art whereby the person of ordinary skill would have selected the components that the inventor selected and used to make the new invention (*C.R. Bard, Inc. v M3 Systems, Inc.*, 157 F.3d 1340, 48 U.S.P.Q.2d 1225 (Fed. Cir. 1998), *cert. denied*, 67 U.S.L.W. 3715 (1999)). The Advisory Action asserted that

Maggio taught that solid phase assay systems employing particles, microplates, discs, tubes or beads "are very convenient to wash thereby reducing labor in assay procedures."

As mentioned above, Maggio teaches that the solid phase can be in the form of particles or preformed into discs, tubes, beads or microplates. Maggio indicates that the advantage of a preformed solid phase is that washing can be carried out very easily whereas, in contrast, washing of particulate solid-phase materials necessitates centrifugation that can be inconvenient. Maggio states as follows in the last two sentences on page 186: "In contrast, washing of particulate solid-phase material necessitates centrifugation which can be inconvenient when large numbers of tests are done. The microplates are very convenient to wash thereby reducing labor on these tests." As can be seen, it is the preformed solid phase such as microplates that Maggio teaches are very convenient. As one might appreciate, in the presently claimed invention, the screening of samples for drugs would be expected to involve a large number of tests.

D. Conclusion

Appellant submits that the rejection of Claims 21-22 as being unpatentable over Oh in view of Maggio cannot be sustained. The combined teachings of the references do not disclose or suggest assaying for a plurality of drugs suspected of being in a sample. The combined teachings of the references do not disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs. Furthermore, the proffered motivation for combining the teachings of the references is based on a misplaced reading of Maggio.

III. Whether the final rejection of Claims 27-34 under 35 U.S.C. §103 should be reversed?

A. The Rejection

Claims 27-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Oh in view of Zuk, *et al.* (U.S. Patent No. 4,281,061) (Zuk). The Advisory Action recognized that Oh fails to teach a kit. However, asserted the Advisory Action, Zuk teaches the

convenience of providing reagents as part of kits and it would have been obvious to one skilled in the art at the time of the invention to formulate the assay of Oh into a kit.

B. Standard of Rejection

The standard of rejection is set forth above with regard to Issue II.

C. Application of Standard to the Claims

(1) Scope and Content of the Art

The disclosure of Oh is set forth above. Zuk discloses methods and compositions for performing homogeneous immunoassays. The methods involve having a signal producing system, which provides a detectable signal, which system includes a macromolecular member. The determination of the analyte, which is a member of a specific binding pair consisting of a ligand and its homologous receptor, is performed by creating an extensive matrix in the assay medium by having in the assay medium in addition to the analyte, ligand labeled with one of the members of the signal producing system, antiligand either present as the analyte or added, a polyvalent receptor for antiligand, the macromolecular member of the signal producing system, and any additional members of the signal producing system. The labeled ligand, antiligand, and polyvalent receptor for the antiligand create a matrix that modulates, e.g. inhibits, the approach of the macromolecular member of the signal producing system to the labeled ligand. The extent and degree of formation of the matrix is dependent upon the concentration of the analyte in the medium. By comparing the signal from an assay medium having an unknown amount of analyte, with a signal obtained from an assay medium having a known amount of analyte, the amount of analyte in the unknown sample may be determined qualitatively or quantitatively. Kits are provided having predetermined amounts of the various reagents to allow for enhanced sensitivity of the method.

(2) Differences between the Art and Claims 27-34

Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of drugs of interest in a sample using multiple sets of reagents, one set for each of

the suspected plurality of drugs. For example, Oh does not disclose or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of adding multiple first reagents, one each for each of the suspected drugs. Zuk discloses formulating reagents into kits for use in immunoassays but does not teach or suggest kits that comprise the presently claimed reagents such as multiple antibodies, one each for each of the suspected drugs, and multiple first reagents, one each for each of the suspected drugs.

(3) Argument

Oh and Zuk, either individually or in combination, do not teach or suggest kits comprising reagents that include multiple antibodies, one each for each of the suspected drugs, and multiple first reagents, one each for each of the suspected drugs. Therefore, a combination of the teachings of the two references cannot result in the presently claimed kits.

As mentioned above, in determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification (*In re Lintner*, *supra*). The teaching of Oh and Zuk fall far short of this required level of disclosure. Oh does not disclose assaying for the presence of one or more of a plurality of drugs in a sample and, thus, formulating the reagents of Oh into kits does not result in the methods of Claims 21 and 22.

The Advisory Action asserted that Appellant's previous arguments were against the references individually and contended that one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references. The Advisory Action cited *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) and *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) in support of the rejection. However, as can be seen upon careful review of those cases, the primary references taught all of the limitations of the claimed invention except one, which was taught in the respective secondary references. However, in the present situation the secondary reference does not teach all of the missing limitations of the primary reference.

Accordingly, combining the teachings of the references does not produce the instant invention.

The Advisory Action contended that Appellant is arguing against the references individually, but the rejections were based on a combination of the references. Appellant wishes to reiterate what was said in Appellant's earlier amendment.

"Applicant further submits that, even if the fanciful combination of the teachings of the references were made, one still would not be in possession of the presently claimed invention. As explained above, none of the references discloses or suggests the reagents employed by Applicant in the present methods. None of the references discloses of suggests, either individually or in combination, a simultaneous determination of the presence of one or more drugs suspected of being present in a sample using the reagents as set forth in the claims." (page 10, last paragraph, Amendment under 37 C.F.R. 1.116).

As can be seen, in mentioning the deficiencies of the individual references, Appellant was providing support for the argument that the combination of the teachings of the references did not yield the present invention.

Accordingly, for the above reasons, it is Appellant's position that the combined teachings of the references do not result in the invention of Claims 27-34. In referring to individual teachings of the references, Appellant is demonstrating why the combined teachings do not yield the present invention. The Office has asserted that the combined teachings do result in the present invention. In doing so, the Office has selectively taken teachings from each of the references and combined them. Appellant is simply showing that such teachings of the references, when combined, cannot produce the present invention.

A *prima facie* case of obviousness has not been made. The question, as framed by the court in *In re Keller*, is whether it would have been obvious to one of ordinary skill in the art, with the references in mind, to do what the inventor has done. For the reasons set forth above, the clear answer to that question is no. Considering the teachings of the references as a whole, the skilled artisan would not have realized a method for screening a sample for one or more of a plurality of drugs suspected of being in the sample using the multiple sets of reagents as defined in the present claims.

In Appellant's Amendment under 37 C.F.R. 1.116, Appellant contended that, in order for one to modify the deficient teachings of the reference to achieve the methods of the present invention, one would have to use Appellant's disclosure because the references do not teach limitations of the presently claimed screening assay. The Advisory Action responded that, so long as it takes into account only knowledge that was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from Appellant's own disclosure, such a reconstruction is proper. However, as Appellant has demonstrated above, the references do not teach certain limitations of the present claims, which are only found in Appellant's disclosure.

The Advisory Action asserted further that the features upon which Appellant relies (i.e., multiple drug detection with multiple antibodies) are not reflected in the claims. The Advisory Action further contended that the instant claims read on not just multiple drug detection but also on single drug detection (one or more drugs in a sample).

Appellant respectfully disagrees with the position of the Advisory Action as discussed above. As can be seen from the above analysis, the assertion in the Advisory Action that the features upon which Appellant relies are not recited in the claims is misplaced. The features relied on are recited in the present claims as discussed above and there is no need to read limitations into the claims from the specification.

D. Conclusion

Appellants respectfully submit that the rejection of Claims 27-34 as being unpatentable over Oh in view of Zuk cannot be maintained. The combined teachings of the references do not disclose or suggest assaying for a plurality of drugs suspected of being in a sample. For example, the combined teachings of the references do not disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs.

RELIEF SOUGHT

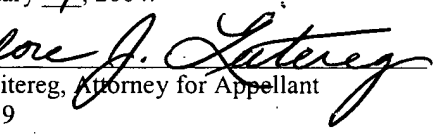
Appellant has demonstrated that Claims 19-20 and 23-26 are patentable under 35 U.S.C. §102(b). Appellant has demonstrated that Claims 21 and 22 are patentable under 35

U.S.C. §103(a). Appellant has demonstrated that Claims 27-34 are patentable under 35 U.S.C. §103(a). Accordingly, Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b), the rejection of Claims 21 and 22 under 35 U.S.C. §103(a) and the rejection of Claims 27-34 under 35 U.S.C. §103(a).

Respectfully submitted,

Theodore J. Leitereg
Attorney for Appellant
Reg. No. 28,319

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on February 4, 2004.



Theodore J. Leitereg, Attorney for Appellant
Reg. No. 28,319

Appendix to Appeal Brief

19. A method for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs, said method comprising:

(a) combining in a medium said sample and an antibody for each of said drugs,

(b) adding to said combination, for each of said drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog, wherein said drug analog competes with said drug, if present, for binding to said antibody for said drug,

(c) adding to said combination a second reagent comprising (i) a second label and (ii) an antibody for said small molecule, wherein said first label and said second label interact in close proximity to produce a predetermined increased amount of signal if one or more of said drugs are present in said sample, wherein said antibody for said drug binds to said drug analog of said first reagent thereby inhibiting the binding of said antibody for said small molecule to said small molecule,

(d) examining said medium for the amount of said signal, said predetermined increased amount thereof being related to the presence of one or more of said drugs in said sample.

20. A method according to Claim 19 wherein said small molecule is selected from the group consisting of drugs, biotin and dyes.

21. A method according to Claim 19 wherein said first reagent is bound to a particle.

22. A method according to Claim 19 wherein said second reagent is bound to a particle.

23. A method according to Claim 19 wherein said first and second labels are selected from the group consisting of a luminescent energy donor and acceptor pair, a

singlet oxygen generator and chemiluminescent reactant pair, and an enzyme pair wherein a product of the first enzyme serves as a substrate for the second enzyme.

24. A method according to Claim 19 wherein one of said first label or said second label is an enzyme and the other of said labels is an enzyme that is different from the first enzyme and a product of the reaction of the enzyme comprising the first label is a substrate for the other of said enzymes.

25. A method according to Claim 19 wherein one of said first label or said second label is a chemiluminescent compound and the other of said labels is a sensitizer.

26. A method according to Claim 19 wherein one of said first label or said second label is an energy donor or acceptor and the other of said labels is a fluorescent compound.

27. A kit for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs, said kit comprising in packaged combination:

(a) an antibody for each of said drugs,

(b) for each of said drugs, a first reagent comprising a first label, a small molecule and a drug analog, and

(c) a second reagent comprising a second label and an antibody for said small molecule, wherein said first label and said second label are capable of interacting in close proximity to modulate a signal if one or more of said plurality of drugs are present in said sample.

28. A kit according to Claim 27 wherein said small molecule is selected from the group consisting of drugs, biotin and dyes.

29. A kit according to Claim 27 wherein said first reagent is bound to a particle.

30. A kit according to Claim 27 wherein said second reagent is bound to a particle.

31. A kit according to Claim 27 wherein said first and second labels are selected from the group consisting of a luminescent energy donor and acceptor pair, a singlet oxygen generator and chemiluminescent reactant pair, and an enzyme pair wherein a product of the first enzyme serves as a substrate for the second enzyme.

32. A kit according to Claim 27 wherein one of said first label or said second label is an enzyme and the other of said labels is an enzyme that is different from the first enzyme and the product of the reaction of the enzyme comprising the first label is a substrate for the other of said enzymes.

33. A kit according to Claim 27 wherein one of said first label or said second label is a chemiluminescent compound and the other of said labels is a sensitizer.

34. A kit according to Claim 27 wherein one of said first label or said second label is an energy donor or acceptor and the other of said labels is a fluorescent compound.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application: 09/691,383

Inventors: Edwin F. Ullman, *et al.*

Filed: October 17, 2000

Title: Simultaneous Screening of Multiple Analytes

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANTS' BRIEF ON APPEAL

This is an appeal from the Final Rejection in the Office Action dated July 14, 2003, by the United States Patent and Trademark Office (the "Office") in the above-identified patent application. A Notice of Appeal was mailed on December 5, 2003.

Jurisdiction over this appeal resides in the Board of Patent Appeals and Interferences under 35 U.S.C. §134.

An oral hearing was not requested.

REAL PARTY IN INTEREST

The real party in interest is Dade Behring Marburg GmbH.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

The claims for consideration on appeal in the present application are Claims 19-34. Claims 1-18 were withdrawn from consideration and were canceled in Appellant's Amendment under 37 C.F.R. §1.116 mailed September 8, 2003. Claim 19 was amended in an Amendment under 37 C.F.R. §1.111 mailed on May 1, 2003. Claims 20-34 are originally filed. The claims as amended are presented herewith in the attached Appendix to Appeal Brief.

STATUS OF THE AMENDMENTS

In an Advisory Action mailed November 13, 2003, the Office indicated that the amendments made to the claims in Appellant's Amendment under 37 C.F.R. §1.116 would be entered.

SUMMARY OF THE INVENTION

The present invention is directed to methods for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of such drugs (p 4, ln 19-20 where p = page and ln = line(s) of the present specification). The sample and an antibody for each of the drugs are combined in a medium (p 9, ln 14-16, and p 10, ln 23). To this combination is added, for each of the drugs, a first reagent comprising a first label, a small molecule and a drug analog (p 11, ln 4-8, p 11, ln 26-27, p 11, ln 26-27). The drug analog competes with the drug, if present, for binding to the antibody for the drug (p 11, ln 18-20). A second reagent is added to the combination where the second reagent comprises a second label and an antibody for the small molecule (p 15, ln 24-28). The first label and the second label interact in close proximity to produce a predetermined increased amount of signal if one or more of the drugs are present in the sample (p 17, ln 3-7). The antibody for the drug binds to the drug analog of the first reagent thereby inhibiting the binding of the antibody for the small molecule to the small molecule (p 27, ln 9-23). The medium is examined for the amount of the signal where a predetermined increased amount of signal is related to the presence of one or more of the drugs in the sample (p 17, ln 7-11).

As indicated in the present specification, high volume screening for drugs of abuse is currently carried out commercially by conducting a series of individual homogeneous immunoassays (EMIT or FPIA). A cut off level is set for each drug, which is used to establish whether a particular result will be defined as positive or negative. It is necessary for testing laboratories to handle separate reagent sets and carry out separate assays for each of the commonly abused drugs in every sample. Typically, the presence of as many as six drugs must be determined. (p 1, ln 22-28)

The present invention permits effective screening of samples for the presence of one or more of a plurality of different analytes (p4, ln 19-20). For example, the present invention provides for screening a sample for one or more of a plurality of drugs of abuse where one is attempting to ascertain whether a sample contains any of the plurality of drugs. For example, one may be interested in determining whether a sample contains one or more of cocaine and morphine. (Example 1 beginning on p 49) In accordance with this exemplary embodiment of the present invention, the sample to be tested is combined in a medium with an antibody for each of the drugs of interest. Accordingly, antibodies for each of cocaine and morphine are added to the medium along with the sample. Also added to the medium, for each of the drugs, is a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog, wherein the drug analog competes with the drug, if present, for binding to the antibody for the drug. Thus, multiple first reagents are added to the medium, one each for each of cocaine and morphine. Also added to the medium is a second reagent comprising (i) a second label and (ii) an antibody for the small molecule, wherein the first label and the second label interact in close proximity to produce a predetermined increased amount of signal if one or more of cocaine and morphine are present in the sample. A single second reagent is added for all of the drug analytes of interest in the sample. The medium is examined for the amount of the signal and a predetermined increased amount of signal is related to the presence of one or more of cocaine and morphine in the sample. The above example is by way of illustration and not limitation.

ISSUES

I. Whether the final rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b) should be reversed?

II. Whether the final rejection of Claims 21 and 22 under 35 U.S.C. §103(a) should be reversed?

III. Whether the final rejection of Claims 27-34 under 35 U.S.C. §103(a) should be reversed?

GROUPING OF CLAIMS

Appellant submits that Claims 19-20 and 23-26 stand or fall together as to the rejection under 35 U.S.C. §102(b).

Appellant submits that Claims 21 and 22 stand or fall together as to the rejection under 35 U.S.C. §103(a).

Appellant submits that Claims 27-34 stand or fall together as to the rejection under 35 U.S.C. §103(a).

ARGUMENT

I. Whether the final rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b) should be reversed?

A. The Rejection

Claims 19-20 and 23-26 were rejected under paragraph (b) of the above code section as being anticipated by Oh, *et al.* (U.S. Patent No. 5,851,778 and WO 89/03041) (collectively, Oh). The above disclosures are essentially duplicative and will be addressed herein collectively as Oh.

The Office asserts that in both the cited references Oh employs a conjugate that comprises three moieties or members to evaluate specific binding partners. Two members of the conjugate are relatively small molecules (less that about 7,000 Daltons). When the conjugate is bound by a macromolecular specific binding partner (sample drug-analyte), it sterically inhibits the binding of other/different macromolecules to another member of the

three-member conjugate. In support of this position, the Office refers to the abstracts of Oh.

An assay protocol, continues the Office, is outlined in figure 1 of both references wherein the assay employs a tridentate complex (referred to by the Office as a first reagent) comprising biotin (first label), first hapten (drug analog), and second hapten (small molecule). The complex is mixed with a sample (free analyte – first hapten/drug), avidin (second label), antibody to the first hapten (antibody to the drug), and an antibody to the second hapten (antibody to the small molecule). The Office further contends that both references evaluate the signal from the target molecules as an increase over background or control signals (predetermined signals).

B. Standard of Rejection

In order to maintain a rejection under 35 U.S.C. §102(b) the Office must first establish a *prima facie* case of anticipation. An invention is anticipated if each and every limitation of the claimed invention is disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994). It is not enough, however, that the prior art reference discloses all the claimed elements in isolation. Rather, as stated by the Federal Circuit, anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention arranged in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 U.S.P.Q. 481 (Fed. Cir. 1984). In addition, the allegedly anticipating reference must be enabling and describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art. *In re Paulsen*, *supra*, at 1673. The anticipation determination is viewed from one of ordinary skill in the art. There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

C. Application of Standard to the Claims

(1) Scope and Content of the Art

Oh discloses a trifunctional conjugate having three chemical moieties attached through a spacer moiety. At least two of the chemical moieties are relatively small molecules. The spacer moiety is selected to impart certain steric properties to the conjugate. In one embodiment the binding of a macromolecular specific binding partner to one of the chemical moieties sterically inhibits the binding of a different macromolecule to another chemical moiety. In another embodiment the binding of a first chemical moiety to a macromolecule restricts the subsequent binding of a second chemical moiety to a proximate location on the same macromolecule. The three chemical moieties are preferably a nitrophenylazido residue, a phenyl boronic acid residue and a solid support or a label such as biotin. The spacer is preferably cysteine, lysine, glutamic acid, pyroglutamic acid, S-acetylmercaptosuccinic anhydride or ω-carbobenzoxylysine. The conjugate is used in immunoassays and for targeted labeling of proteins. In an assay, a sample is contacted with the conjugate, a limited quantity of analyte binding partner and an excess of small molecule binding partner. Presence of the analyte is determined by detecting the amount of analyte binding partner diverted away from analyte attached to the spacer of the conjugate.

(2) Differences between the Art and Claims 19-20 and 23-26

Oh's assay is directed to the determination of a single analyte in a sample using only reagents for the detection of a single analyte. On the other hand, the present invention is directed to an assay for the determination of one or more of a plurality of drugs of interest in a sample. The present methods include the step of adding multiple antibodies, one each for each of the drugs suspected of being in the sample. Additionally, the present methods include the step of adding multiple first reagents, one each for each of the drugs suspected of being in the sample.

As can be seen, for instance, from Oh's examples, the patentee conducts assays for a single analyte (e.g., theophylline or theophylline-amine) using only reagents for the detection of such single analyte. See, for example, column 37, lines 34-48, in which an aliquot of the patient's sample is combined with an aliquot of the tridentate solution. The

combined solution is then incubated with the optimized antibody solution. Then, an aliquot of the optimized proximity label solution is added. After inclusion of the substrate solution, signal is measured. The patentee indicates that the same procedure is repeated for various dilutions of a theophylline or theophylline-amine standard. In this way, continues the patentee, a standard curve is obtained and the concentration of theophylline or theophylline-amine in the sample can be extrapolated.

(3) Argument

As indicated above, Oh does not disclose each and every element of the claimed invention of the above claims. One skilled in the art, reading the disclosure of Oh, would not be placed in possession of a method such as claimed in the present application. The skilled artisan would recognize the significant difference between Oh's method of detecting a single analyte versus the method of the invention wherein a sample is screened for the presence of one or more drugs using multiple reagents, one set of reagents for each of the drugs suspected of being present in the sample. As the court has held, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention (*Scripps Clinic & Research Found. v. Genentech Inc.*). This is not the case in the present situation.

The Advisory Action particularly focused attention on Appellant's statement that Oh does not disclose or suggest adding multiple antibodies, one each for each of the suspected analytes. The Advisory Action contended that Oh teaches the use of two antibodies (multiple antibodies) in Oh's assay of figure 1, namely, an antibody to a first hapten and an antibody to a second hapten.

However, Appellant's argument was that Oh does not disclose or suggest adding multiple antibodies, one each for each of the drugs. Oh does not teach such a method and reagents. Oh's assay, to which the Advisory Action referred, uses an antibody to a first hapten and an antibody to a second hapten. Nowhere does Oh disclose multiple antibodies, one each for each of the drugs suspected of being in the sample. Oh indicates that the first tridentate member is biotin, the second tridentate member is a first hapten, which is identical to the analyte of interest, and the third tridentate member is a second hapten

different from the analyte of interest (column 15, last line, to column 16, line 6). Accordingly, in the example shown Oh uses only one antibody for an analyte, which is in keeping with his teaching of an assay for the detection of a single analyte, not one or more of a plurality of analytes. Oh does not disclose using multiple antibodies, one each for the detection of multiple suspected analytes, as claimed by Appellant.

The Advisory Action asserted further that the features upon which Appellant relies (i.e., multiple drug detection with multiple antibodies) are not reflected in the claims. The Advisory Action further contended that the instant claims read on not just multiple drug detection but also on single drug detection (one or more drugs in a sample).

Appellant respectfully disagrees with the position of the Advisory Action. The instant claims recite in the preamble "determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs." (emphasis added) Furthermore, the body of the claim recites "(a) combining in a medium said sample and an antibody for each of said drugs, (b) adding to said combination, for each of said drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog." (emphasis added) In this way, Appellant's method screens a sample for the presence of one or more drugs in a sample suspected of containing a plurality of drugs to determine if any of such drugs are in the sample. Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of analytes of interest in a sample. Oh does not disclose or suggest adding multiple antibodies, one each for each of the suspected analytes. Oh fails to disclose or suggest adding multiple first reagents, one each for each of the suspected analytes. Accordingly, Oh does not teach an assay for the determination of one or more drugs in a sample suspected of containing any of a plurality of the drugs. As mentioned above, anticipation requires the presence, in a single prior art reference disclosure, of each and every element of the claimed invention arranged in the claim (*Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., supra*). The teaching of Oh falls far short of this required level of disclosure.

As can be seen from the above analysis, the assertion in the Advisory Action that the features upon which Appellant relies are not recited in the claims is misplaced. The features relied on are recited in the present claims as discussed above and there is no need

to read limitations into the claims from the specification. Accordingly, *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993) is not applicable to the present situation.

The Advisory Action further argued that, even though every limitation of a claimed process is not disclosed in a prior art reference, anticipation can be found on the inferences which one skilled in the art would reasonably expect to draw therefrom. The Advisory Action also referred to Oh at column 16, lines 30-49, as teaching that other drugs can be effectively assayed in competition by the Oh method. However, the cited passage does not teach an assay as presently claimed, which involves combining a sample with an antibody for each of the drugs suspected of being in the sample and adding to the combination, for each of the drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog. Oh is merely indicating that his approach may be used to assay for a drug other than theophylline.

Oh's use of the term "competitively" must be viewed in context. The language of Oh that recites "in a competitively modulated assay such as NIIA" would not be interpreted by one skilled in the art beyond what is taught by Oh. At column 15, lines 21-25, Oh indicates that the tridentate is particularly useful in competitively modulated assays where the analyte of interest is a hapten, or analog thereof. The competitively modulated assay to which Oh refers is also discussed at column 14, lines 36-57, and column 15, lines 14-21. It is readily seen that the use of Oh's tridentate involves steric hindrance or inhibition. The binding of a macromolecule to the second (modulating) member of the tridentate prevents the simultaneous binding of the first and/or third tridentate members to their corresponding macromolecules. In this way, Oh's method is applicable in the area of competitively modulated immunoassays. For the reasons given above, Oh does not teach that "other drugs can be effectively assayed in competition."

D. Conclusion

Appellant has demonstrated above that the rejection of Claims 19-20 and 23-26 as anticipated by Oh cannot be sustained. The Oh references do not disclose each and every element of the claimed invention as explained above. At the very least, Oh does not

disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs.

II. Whether the final rejection of Claims 21-22 under 35 U.S.C. §103 should be reversed?

A. The Rejection

Claims 21 and 22 were rejected under 35 U.S.C. 103(a) as being unpatentable over Oh in view of Maggio (Enzyme Immunoassay, CRC Press 1980, pages 186-187). The Advisory Action argued that Oh differs from the instant invention in not specifically teaching the detection assay employing a solid phase such as particles. However, asserted the Advisory Action, Maggio discloses enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase. The Advisory Action concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use solid phase/particles as taught by Maggio in the assay method to detect the drug interaction of Oh.

B. Standard of Rejection

In order to maintain a rejection under 35 U.S.C. §103 the Office must first establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification. *In re Lintner*, 458 F.2d 1013, 173 U.S.P.Q. 560 (C.C.P.A. 1972). In asserting a *prima facie* case of obviousness involving more than one reference, the Office must show some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references offered by the Office as evidence of obviousness. *In re Lalu*, 747 F.2d 703; 223 U.S.P.Q. 1257 (Fed. Cir. 1984). In determining the scope and content of the prior art, references must be considered in their

entirety, as a whole, including portions that would lead away from the claimed invention. *In re Panduit*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed Cir. 1987). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine, supra.*

C. Application of Standard to the Claims

(1) Scope and Content of the Art

The disclosure of Oh is set forth above. Maggio teaches separation steps with special reference to solid phases including beads. The reference indicates that, in virtually all of the enzyme-immunoassays discussed in the reference, either the antigen or antibody may be immobilized onto a solid phase. The solid phase can be in the form of particles or preformed into discs, tubes, beads or microplates. Maggio indicates that the advantage of a preformed solid phase is that washing can be carried out very easily whereas, in contrast, washing of particulate solid-phase materials necessitates centrifugation that can be inconvenient.

(2) Differences between the Art and Claims 21-22

Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of drugs of interest in a sample using multiple sets of reagents, one set for each of the suspected plurality of drugs. Oh does not disclose or suggest the step of adding multiple antibodies, one each for each of the suspected drugs. Oh fails to disclose or suggest the step of adding multiple first reagents, one each for each of the suspected drugs. Maggio discloses the use of particles in immunoassays but does not teach or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of adding multiple first reagents, one each for each of the suspected drugs.

(3) Argument

Oh and Maggio, either individually or in combination, do not teach or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of

adding multiple first reagents, one each for each of the suspected drugs. Therefore, a combination of the teachings of the two references cannot result in the presently claimed methods. Furthermore, even if for the sake of argument the combined teachings could result in the presently claimed methods, Maggio teaches away from making the combination suggested in the Advisory Action. As mentioned above, Maggio teaches the preference for a preformed solid phase over a particulate solid phase. Therefore, the skilled artisan, if inclined to make a combination of teachings, would be inclined to use discs, plates and the like, rather than particles, in the method of Oh. In any event, as mentioned above, the combined teachings of Oh and Maggio do not produce the presently claimed methods because the combined teachings still do not contain all of the elements of the presently claimed methods.

As mentioned above, in determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification (*In re Lintner*, *supra*). The teaching of Oh and Maggio fall far short of this required level of disclosure. Oh does not disclose assaying for the presence of one or more of a plurality of drugs in a sample and, thus, using particles in the method of Oh does not result in the methods of Claims 21 and 22.

Furthermore, as mentioned above, in determining the scope and content of the prior art, references must be considered in their entirety, as a whole, including portions that would lead away from the claimed invention (*In re Panduit*, *supra*). In the present situation, it would not be unreasonable for the skilled artisan to conclude that Maggio actually does teach away from the methods of the invention of Claims 21 and 22.

Appellant previously submitted that it has been held that there must be some suggestion, motivation or teaching in the prior art whereby the person of ordinary skill would have selected the components that the inventor selected and used to make the new invention (*C.R. Bard, Inc. v M3 Systems, Inc.*, 157 F.3d 1340, 48 U.S.P.Q.2d 1225 (Fed. Cir. 1998), *cert. denied*, 67 U.S.L.W. 3715 (1999)). The Advisory Action asserted that

Maggio taught that solid phase assay systems employing particles, microplates, discs, tubes or beads "are very convenient to wash thereby reducing labor in assay procedures."

As mentioned above, Maggio teaches that the solid phase can be in the form of particles or preformed into discs, tubes, beads or microplates. Maggio indicates that the advantage of a preformed solid phase is that washing can be carried out very easily whereas, in contrast, washing of particulate solid-phase materials necessitates centrifugation that can be inconvenient. Maggio states as follows in the last two sentences on page 186: "In contrast, washing of particulate solid-phase material necessitates centrifugation which can be inconvenient when large numbers of tests are done. The microplates are very convenient to wash thereby reducing labor on these tests." As can be seen, it is the preformed solid phase such as microplates that Maggio teaches are very convenient. As one might appreciate, in the presently claimed invention, the screening of samples for drugs would be expected to involve a large number of tests.

D. Conclusion

Appellant submits that the rejection of Claims 21-22 as being unpatentable over Oh in view of Maggio cannot be sustained. The combined teachings of the references do not disclose or suggest assaying for a plurality of drugs suspected of being in a sample. The combined teachings of the references do not disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs. Furthermore, the proffered motivation for combining the teachings of the references is based on a misplaced reading of Maggio.

III. Whether the final rejection of Claims 27-34 under 35 U.S.C. §103 should be reversed?

A. The Rejection

Claims 27-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Oh in view of Zuk, *et al.* (U.S. Patent No. 4,281,061) (Zuk). The Advisory Action recognized that Oh fails to teach a kit. However, asserted the Advisory Action, Zuk teaches the

convenience of providing reagents as part of kits and it would have been obvious to one skilled in the art at the time of the invention to formulate the assay of Oh into a kit.

B. Standard of Rejection

The standard of rejection is set forth above with regard to Issue II.

C. Application of Standard to the Claims

(1) Scope and Content of the Art

The disclosure of Oh is set forth above. Zuk discloses methods and compositions for performing homogeneous immunoassays. The methods involve having a signal producing system, which provides a detectable signal, which system includes a macromolecular member. The determination of the analyte, which is a member of a specific binding pair consisting of a ligand and its homologous receptor, is performed by creating an extensive matrix in the assay medium by having in the assay medium in addition to the analyte, ligand labeled with one of the members of the signal producing system, antiligand either present as the analyte or added, a polyvalent receptor for antiligand, the macromolecular member of the signal producing system, and any additional members of the signal producing system. The labeled ligand, antiligand, and polyvalent receptor for the antiligand create a matrix that modulates, e.g. inhibits, the approach of the macromolecular member of the signal producing system to the labeled ligand. The extent and degree of formation of the matrix is dependent upon the concentration of the analyte in the medium. By comparing the signal from an assay medium having an unknown amount of analyte, with a signal obtained from an assay medium having a known amount of analyte, the amount of analyte in the unknown sample may be determined qualitatively or quantitatively. Kits are provided having predetermined amounts of the various reagents to allow for enhanced sensitivity of the method.

(2) Differences between the Art and Claims 27-34

Oh fails to disclose or suggest an assay for the determination of one or more of a plurality of drugs of interest in a sample using multiple sets of reagents, one set for each of

the suspected plurality of drugs. For example, Oh does not disclose or suggest the step of adding multiple antibodies, one each for each of the suspected drugs, or the step of adding multiple first reagents, one each for each of the suspected drugs. Zuk discloses formulating reagents into kits for use in immunoassays but does not teach or suggest kits that comprise the presently claimed reagents such as multiple antibodies, one each for each of the suspected drugs, and multiple first reagents, one each for each of the suspected drugs.

(3) Argument

Oh and Zuk, either individually or in combination, do not teach or suggest kits comprising reagents that include multiple antibodies, one each for each of the suspected drugs, and multiple first reagents, one each for each of the suspected drugs. Therefore, a combination of the teachings of the two references cannot result in the presently claimed kits.

As mentioned above, in determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed substitution, combination or other modification (*In re Lintner*, *supra*). The teaching of Oh and Zuk fall far short of this required level of disclosure. Oh does not disclose assaying for the presence of one or more of a plurality of drugs in a sample and, thus, formulating the reagents of Oh into kits does not result in the methods of Claims 21 and 22.

The Advisory Action asserted that Appellant's previous arguments were against the references individually and contended that one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references. The Advisory Action cited *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) and *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) in support of the rejection. However, as can be seen upon careful review of those cases, the primary references taught all of the limitations of the claimed invention except one, which was taught in the respective secondary references. However, in the present situation the secondary reference does not teach all of the missing limitations of the primary reference.

Accordingly, combining the teachings of the references does not produce the instant invention.

The Advisory Action contended that Appellant is arguing against the references individually, but the rejections were based on a combination of the references. Appellant wishes to reiterate what was said in Appellant's earlier amendment.

"Applicant further submits that, even if the fanciful combination of the teachings of the references were made, one still would not be in possession of the presently claimed invention. As explained above, none of the references discloses or suggests the reagents employed by Applicant in the present methods. None of the references discloses of suggests, either individually or in combination, a simultaneous determination of the presence of one or more drugs suspected of being present in a sample using the reagents as set forth in the claims." (page 10, last paragraph, Amendment under 37 C.F.R. 1.116).

As can be seen, in mentioning the deficiencies of the individual references, Appellant was providing support for the argument that the combination of the teachings of the references did not yield the present invention.

Accordingly, for the above reasons, it is Appellant's position that the combined teachings of the references do not result in the invention of Claims 27-34. In referring to individual teachings of the references, Appellant is demonstrating why the combined teachings do not yield the present invention. The Office has asserted that the combined teachings do result in the present invention. In doing so, the Office has selectively taken teachings from each of the references and combined them. Appellant is simply showing that such teachings of the references, when combined, cannot produce the present invention.

A *prima facie* case of obviousness has not been made. The question, as framed by the court in *In re Keller*, is whether it would have been obvious to one of ordinary skill in the art, with the references in mind, to do what the inventor has done. For the reasons set forth above, the clear answer to that question is no. Considering the teachings of the references as a whole, the skilled artisan would not have realized a method for screening a sample for one or more of a plurality of drugs suspected of being in the sample using the multiple sets of reagents as defined in the present claims.

In Appellant's Amendment under 37 C.F.R. 1.116, Appellant contended that, in order for one to modify the deficient teachings of the reference to achieve the methods of the present invention, one would have to use Appellant's disclosure because the references do not teach limitations of the presently claimed screening assay. The Advisory Action responded that, so long as it takes into account only knowledge that was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from Appellant's own disclosure, such a reconstruction is proper. However, as Appellant has demonstrated above, the references do not teach certain limitations of the present claims, which are only found in Appellant's disclosure.

The Advisory Action asserted further that the features upon which Appellant relies (i.e., multiple drug detection with multiple antibodies) are not reflected in the claims. The Advisory Action further contended that the instant claims read on not just multiple drug detection but also on single drug detection (one or more drugs in a sample).

Appellant respectfully disagrees with the position of the Advisory Action as discussed above. As can be seen from the above analysis, the assertion in the Advisory Action that the features upon which Appellant relies are not recited in the claims is misplaced. The features relied on are recited in the present claims as discussed above and there is no need to read limitations into the claims from the specification.

D. Conclusion

Appellants respectfully submit that the rejection of Claims 27-34 as being unpatentable over Oh in view of Zuk cannot be maintained. The combined teachings of the references do not disclose or suggest assaying for a plurality of drugs suspected of being in a sample. For example, the combined teachings of the references do not disclose or suggest adding multiple antibodies, one each for each of the suspected drugs, or multiple first reagents, one each for each of the suspected drugs.

RELIEF SOUGHT

Appellant has demonstrated that Claims 19-20 and 23-26 are patentable under 35 U.S.C. §102(b). Appellant has demonstrated that Claims 21 and 22 are patentable under 35

U.S.C. §103(a). Appellant has demonstrated that Claims 27-34 are patentable under 35 U.S.C. §103(a). Accordingly, Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the rejection of Claims 19-20 and 23-26 under 35 U.S.C. §102(b), the rejection of Claims 21 and 22 under 35 U.S.C. §103(a) and the rejection of Claims 27-34 under 35 U.S.C. §103(a).

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on February 4, 2004.

Theodore J. Leitereg

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Appendix to Appeal Brief

19. A method for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs, said method comprising:

(a) combining in a medium said sample and an antibody for each of said drugs,

(b) adding to said combination, for each of said drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog, wherein said drug analog competes with said drug, if present, for binding to said antibody for said drug,

(c) adding to said combination a second reagent comprising (i) a second label and (ii) an antibody for said small molecule, wherein said first label and said second label interact in close proximity to produce a predetermined increased amount of signal if one or more of said drugs are present in said sample, wherein said antibody for said drug binds to said drug analog of said first reagent thereby inhibiting the binding of said antibody for said small molecule to said small molecule,

(d) examining said medium for the amount of said signal, said predetermined increased amount thereof being related to the presence of one or more of said drugs in said sample.

20. A method according to Claim 19 wherein said small molecule is selected from the group consisting of drugs, biotin and dyes.

21. A method according to Claim 19 wherein said first reagent is bound to a particle.

22. A method according to Claim 19 wherein said second reagent is bound to a particle.

23. A method according to Claim 19 wherein said first and second labels are selected from the group consisting of a luminescent energy donor and acceptor pair, a

singlet oxygen generator and chemiluminescent reactant pair, and an enzyme pair wherein a product of the first enzyme serves as a substrate for the second enzyme.

24. A method according to Claim 19 wherein one of said first label or said second label is an enzyme and the other of said labels is an enzyme that is different from the first enzyme and a product of the reaction of the enzyme comprising the first label is a substrate for the other of said enzymes.

25. A method according to Claim 19 wherein one of said first label or said second label is a chemiluminescent compound and the other of said labels is a sensitizer.

26. A method according to Claim 19 wherein one of said first label or said second label is an energy donor or acceptor and the other of said labels is a fluorescent compound.

27. A kit for determining the presence of one or more drugs in a sample suspected of containing any of a plurality of said drugs, said kit comprising in packaged combination:

(a) an antibody for each of said drugs,

(b) for each of said drugs, a first reagent comprising a first label, a small molecule and a drug analog, and

(c) a second reagent comprising a second label and an antibody for said small molecule, wherein said first label and said second label are capable of interacting in close proximity to modulate a signal if one or more of said plurality of drugs are present in said sample.

28. A kit according to Claim 27 wherein said small molecule is selected from the group consisting of drugs, biotin and dyes.

29. A kit according to Claim 27 wherein said first reagent is bound to a particle.

30. A kit according to Claim 27 wherein said second reagent is bound to a particle.

31. A kit according to Claim 27 wherein said first and second labels are selected from the group consisting of a luminescent energy donor and acceptor pair; a singlet oxygen generator and chemiluminescent reactant pair, and an enzyme pair wherein a product of the first enzyme serves as a substrate for the second enzyme.

32. A kit according to Claim 27 wherein one of said first label or said second label is an enzyme and the other of said labels is an enzyme that is different from the first enzyme and the product of the reaction of the enzyme comprising the first label is a substrate for the other of said enzymes.

33. A kit according to Claim 27 wherein one of said first label or said second label is a chemiluminescent compound and the other of said labels is a sensitizer.

34. A kit according to Claim 27 wherein one of said first label or said second label is an energy donor or acceptor and the other of said labels is a fluorescent compound.

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